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| 09/319,521      | 06/04/1999  | MARK F. PITTENGER    | 640100-326          | 3211             |

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1644

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 09/319,521  
Filing Date: June 04, 1999  
Appellant(s): PITTENGER ET AL.

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Raymond J. Lillie  
For Appellant

### **EXAMINER'S ANSWER**

This is in response to the appeal brief filed 07/10/06 appealing from the Office action mailed 06/29/05.

#### **(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

#### **(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

#### **(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

#### **(4) Status of Amendments After Final**

No amendment after final has been filed.

Art Unit: 1644

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

US Patent 5,908,784

US Patent 5,368,858

Cellgro Catalog, 2001

US Biological Catalogue , 2004

Williams et al ., Tissue Engineering, 2003, Vol.9 N.4, pages 679-688

### **(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

#### **Issue I Rejection under 35 U.S.C. 102(e)**

Claims 60-79 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,908,784 as evidenced by Cellgro catalog, US Biological Cataloge (2004) and Williams et al.

The US Patent 784 teaches a process for producing chondrocytes from mesenchymal stem cells and a process for inducing chondrogenesis in mesenchymal stem cells comprising culturing human mesenchymal stem cells in vitro in a three dimensional format with at least one chondroinductive agent. US Patent '784 teaches that any serum-free animal medium can be used, including DMEM, IMEM, Mc Coy5A and BGJ<sub>b</sub> medium (see column 4, lines 25-35 in particular). The mesenchymal stem cells are preferably isolated, culture expanded human mesenchymal stem cells in a chemically defined serum free environment and are condensed in close proximity, such as in the form of a three - dimensional cell mass, e.g. packed cells or a centrifugal pellet or in a ceramic cube. The chondroinductive agent is preferably selected, individually or in combination from the group consisting of: 1) a glucocorticoid such as dexamethasone; ii) a member of the transforming growth factor beta super family (TGF- $\beta$ ) such as BMP-2 or BMP-4, TGF- $\beta$ 1; iii) a component of the collagenous extracellular matrix such as collagen 1; and IV) a vitamin A analog such as retinoic acid. Particularly preferred is the combination of dexamethasone and TGF-beta-1, (see entire patent, especially column 2, lines 5-33, and column 9, lines 45-50).

As evidence by Cellgro Catalog, US Biological Catalog and Williams et al., the glucose content in DMEM, IMEM, Mc Coy5A is about 4.5 g/l. Said concentration is a species of genus glucose concentration from about 3 g/l to about 7 g/l as claimed in claims 60-79.

Art Unit: 1644

Moreover, as is evidenced by Williams et al., one skilled in the art at the time the invention was made would know that a chondrogenic medium inherently consists of high -glucose Dulbecco's modified Eagle's medium (DMEM) ( see entire document, page 681 in particular).

A species will anticipate a claim to a genus. See MPEP 2131.02.

The reference teaching anticipates the claimed invention.

## **Issue II. Rejection under 35 U.S.C. 103(a)**

Claims 80- 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,908,784 as evidenced by Cellgro catalog , US Biological Cataloge (2004) and Williams et al., in view of US Patent 5,368,858.

The teaching of US Patent 5,908,784, has been discussed, supra.

The US Patent '784, does not explicitly teach the use of TGF- $\beta$ 3.

US Patent '858 teaches the use of TGF- $\beta$ 3 in a method of proliferating chondrocytes and states that the activity among members of the TGF- $\beta$  family are similar (see entire patent including column 8, lines 7-24). US Patent '784 also teaches that mesenchymal cells when exposed to TGF- $\beta$ 3 will be transformed into a chondrocytes (see entire patent, including column, lines 28-33 and 59-67, and claim 1). US Patent '858 also teaches that the dosages TGF- $\beta$ 3 is 2-10 ng/ml ( see entire patent, column 18 and claim 1 in particular).

Art Unit: 1644

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent ' 858 to those of US Patent 784 to obtain a claimed process for producing chondrocytes from mesenchymal stem cells using TGF- $\beta$ 3 as one of the chondrioinductive agent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because the activity among members of the TGF- $\beta$  family are similar, that TGF- $\beta$ 3 can be used in a method of proliferating chondrocytes, and that mesenchymal cells when exposed to TGF- $\beta$ 3 will be transformed into a chondrocytes as taught by US Patent 858. Thus one member of TGF- $\beta$  family, i.e. TGF- $\beta$ 1 can be substituted for other member of TGF- $\beta$  family, i.e. TGF- $\beta$ 3 in a process for producing chondrocytes from mesenchymal stem cells taught by US Patent '784. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### **(10) Response to Argument**

#### **Issue I Rejection under 35 U.S.C. 102(e)**

Claims 60-79 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,908,784 as evidenced by Cellgro catalog, US Biological Cataloge (2004) and Williams et al.

At page 5 of the Brief, Appellant argues that although US Patent '784 lists DMEM as an example of a medium which may be used to promote chondrogenesis of mesenchymal stem cells, DMEM does not inherently have a simple sugar concentration of from 3g/l to 7 g/l. Appellant further asserts that the Examiner even admits at page 3, lines 1-4 of the Final Office Action that there are examples of DMEM that have a glucose concentration of only 1g/l, including the DMEM used in Patent '784.

Appellant further asserts that the examiner relies on an additional references in order to formulate the rejection. US Biological Catalog and Cellgro catalog provide no information as to the level of skill in the art with respect to producing chondrocytes from a culture of mesenchymal stem cells. Cellgro and US Biological Catalog does not provide any suggestion to one of ordinary skill in the art as to the types of the cells which may be cultured in DMEM including 4.5 g/l. Williams does not disclose all of the elements of Appellant's claims 60-79.

Contrary to Appellants assertion it is noted that at page 3, lines 1-4 of the Final Office Action, mailed on 06/29/05 the Examiner never admits that the glucose concentration of DMEM used in Patent '784 was 1 g/l. Moreover, the examiner clearly stated that at the time the invention



Art Unit: 1644

was made one skill in the art would immediately recognized that DMEM medium used in US Patent'784 is the DMEM that has glucose concentration of 4.5 g/l. The examiner used evidential references of US Biological Catalog and Cellgro catalog to support his position. In this regards it is noted that the Examiner does not relies of these references to formulate the rejection. Said references was used to show that one skill in the art would know that the DMEM medium has glucose content of 4.5 g/l. It was also used to show that one skill in the art would know that the DMEM medium with 1 g/l of glucose is a very special type of medium which is termed **low-glucose DMEM**. In other words, said evidential references have been used to show that at the time the invention was made skill artisan would know that DMEM medium, i.e. **Dulbecco's Modified Eagles Medium** would inherently have 4.5 g/l of glucose. Actually, one skill in the art would know that the name **modified** indicated alteration in glucose content in the medium, since original Dulbecco's Eagle Medium that was used since 1959 contains 1g/l of glucose. At the time the invention was made, one skill in the art would immediately recognized that the term "**DMEM**", means the medium with glucose content of 4.5 g/l; while the term "**low-glucose DMEM**" means the medium with 1g/l of glucose and the term "**high-glucose DMEM**" means the medium with 10 g/l of glucose. US Biological Catalog and Cellgro catalog have been used to support this general knowledge in the art. Thus said references do not have to provide any suggestion or motivation to use DMEM or any other medium to producing chondrocytes from a culture of mesenchymal stem cells as Appellant asserted.

With regards to the issue that Williams does not disclose all of the elements of Appellant's claims 60-79.

Said references has been used as an **evidential** references **not as a prior art references**, thus it should not disclosed all elements of Appellant's claims. As in the case with US Biological Catalog and Cellgro catalog, said reference has been used only to support the examiner position that at the time the invention was made one skilled in the art would know that chondrogenic medium consisted of high-glucose DMEM, i.e. DMEM with 10 g/l of glucose.

Art Unit: 1644

**Issue II. Rejection under 35 U.S.C. 103(a)**

Claims 80- 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,908,784 as evidenced by Cellgro catalog , US Biological Cataloge (2004) and Williams et al., in view of US Patent 5,368,858.

At page 7 of the Brief, Appellant asserts that since Cellgro catalog , US Biological Cataloge and Williams are not prior art references they can not be used in the rejection in combination with any other references.

At page 8 of the Brief Appellant asserts that US Patent '784 does not disclosed or even suggest that TGF- $\beta$ 3 may be used as a chondronductive agent.

US Patent '858, though teach that TGF- $\beta$ 3 may be used in composition for transforming repair cells into chondrocytes, it does not teach a chemically defined minimal essential medium , containing glucose from 3g/l to 7 g/l.

Contrary to Appellants assertion as has been discussed supra, it is the Examiner position that Cellgro catalog , US Biological Cataloge and Williams et al., are not prior art references but evidential references that has been used by the Examiner to support his position.

With regard to the issue that US Patent '784 does not disclosed or even suggest that TGF- $\beta$ 3 may be used as a chondronductive agent and that US Patent '858 does not teach minimal essential medium , containing glucose from 3g/l to 7 g/l.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the

Art Unit: 1644

references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

The teaching of US Patent 5,908,784, has been discussed, supra.

The US Patent '784, does not explicitly teach the use of TGF- $\beta$ 3.

US Patent '858 teaches the use of TGF- $\beta$ 3 in a method of proliferating chondrocytes and states that the activity among members of the TGF- $\beta$  family are similar (see entire patent including collumn 8, lines 7-24). US Patent '784 also teaches that mesenchymal cells when exposed to TGF- $\beta$ 3 will be transformed into a chondrocytes (see entire patent, including column, lines 28-33 and 59-67, and claim 1). US Patent '858 also teaches that the dosages TGF- $\beta$ 3 is 2-10 ng/ml ( see entire patent, column 18 and claim 1 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent ' 858 to those of US Patent 784 to obtain a claimed process for producing chondrocytes from mesenchymal stem cells using TGF- $\beta$ 3 as one of the chondrioinductive agent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because the activity among members of the TGF- $\beta$  family are similar, that TGF- $\beta$ 3 can

Art Unit: 1644

be used in a method of proliferating chondrocytes, and that mesenchymal cells when exposed to TGF- $\beta$ 3 will be transformed into a chondrocytes as taught by US Patent 858. Thus one member of TGF- $\beta$  family, i.e. TGF- $\beta$ 1 can be substituted for other member of TGF- $\beta$  family, i.e. TGF- $\beta$ 3 in a process for producing chondrocytes from mesenchymal stem cells taught by US Patent '784. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

#### **(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

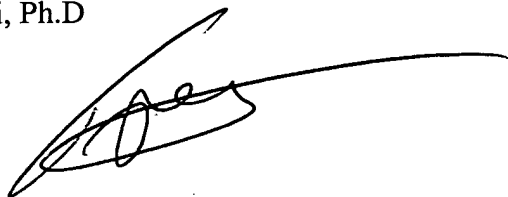
For the above reasons, it is believed that the rejections should be sustained.

Art Unit: 1644

Respectfully submitted,

Michail Belyavskiy, Ph.D

Art Unit 1644

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Conferees:

A handwritten signature in black ink, appearing to be 'Christina Chan', written in a cursive style.

Christina Chan

SPE, Art Unit 1644

A handwritten signature in black ink, appearing to be 'Long Le', written in a cursive style.

Long Le

SPE, Art Unit 1641